Growth Factors: Colony-stimulating Factors

Myeloma patients may have low numbers of white blood cells (WBCs) as a result of chemotherapy or as a result of myeloma cells crowding out the normal blood-producing cells in the bone marrow. In either case, a reduced WBC count can lead to an increased risk of infection.

Colony-stimulating factors (CSFs) are medications used to increase the number of WBCs. This section explains what CSFs are, when they may be used, and their benefits in myeloma.

What Are Colony-stimulating Factors?

Growth factors known as colony-stimulating factors stimulate production of infection-fighting WBCs. One type of WBC that is particularly important in fighting off infection is called a neutrophil. Neutrophils, also known as granulocytes, account for the majority of WBCs in the body. When neutrophil levels drop below normal (a condition known as neutropenia), the body is less able to fight off infection. Another type of WBC is a monocyte/macrophage. These cells also help fight infection.

There are two main types of colony-stimulating factors used therapeutically in myeloma:

- Granulocyte colony-stimulating factor (G-CSF) stimulates the production of neutrophils (granulocytes).
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the production of both neutrophils and macrophages.

Examples of Colony-stimulating Factors

Examples of G-CSFs available in the United States include filgrastim (Neupogen®) and pegfilgrastim (Neulasta®). An example of GM-CSF is sargramostim (Leukine®). Each varies slightly in its effect in the body and in the indications in which they are marketed for usage (see table below). However, it is possible that myeloma patients may receive any 1 of these agents.

Colony-stimulating Factors Used Therapeutically in Myeloma

Brand name (Generic name) Scientific name	Manufacturer	Effect in the body	Approved uses
Leukine (sargramostim)	Berlex	Stimulates the production of	• To shorten time to neutrophil recovery and

Brand name (Generic name) Scientific name	Manufacturer	Effect in the body	Approved uses
Granulocyte-macrophage CSF (GM-CSF)		WBCs known as granulocytes and macrophages	decrease infection in older patients with acute myelogenous leukemia (AML) following chemotherapy • Stem cell mobilization prior to stem cell transplant (SCT) • To reduce the duration of neutropenia in cancer patients receiving SCTs • To prolong survival in patients experiencing engraftment delay or failure following SCT
Neupogen (filgrastim) G-CSF	Amgen Inc.	Stimulates the production of WBCs known as granulocytes	• To decrease infection in patients receiving chemotherapy that suppresses the bone marrow, including patients with AML • Stem cell mobilization prior to SCT • To reduce the duration of neutropenia in cancer patients receiving SCTs • Treatment for severe chronic neutropenia
Neulasta (pegfilgrastim) Pegylated G-CSF	Amgen Inc.	Stimulates the production of WBCs known as granulocytes; long-acting form of filgrastim	To decrease infection in patients receiving chemotherapy that suppresses the bone marrow

Granocyte® (lenograstim, glycosylated G-CSF, Sanofi Aventis) is a type of long-acting C-CSF that is marketed outside of the US.

When Are Colony-stimulating Factors Used?

Many types of chemotherapy suppress the bone marrow and can lead to low neutrophil counts that can be associated with fever, a condition known as febrile neutropenia. In many instances, febrile neutropenia means that there is an infection. Patients receiving chemotherapy may receive colony-stimulating factors prophylactically to increase the number of neutrophils and to reduce the chance of febrile neutropenia and infection. Keeping white blood cell counts up and preventing infection can help keep patients on track with their chemotherapy dose and schedule, which helps ensure that they receive the maximum benefit from their therapy.

Patients who are having their stem cells harvested prior to high-dose chemotherapy and autologous peripheral blood stem cell transplantation may also receive CSFs prior to stem cell collection. Administration of these growth factors helps "mobilize" their stem cells — that is, move the stem cells from the bone marrow into the blood stream to increase the number of stem cells collected for the transplant. Chemotherapy may be administered prior to or along with colony-stimulating factors to further increase the number of cells collected following mobilization.

CSFs may also be administered after high-dose chemotherapy and stem cell transplatation to help speed up the production of white blood cells by the transplanted bone marrow and allow for a faster recovery. A faster recovery reduces the chance of infection, need for antibiotics, and length of hospital stay.

- Get more information on Stem Cell Transplantation

Guidelines for Use of Colony-stimulating Factors

In 2000, the American Society of Clinical Oncology (ASCO) updated their recommendations for the use of CSFs in patients with cancer. (Ozer et al. *J Clin Oncol.* 2000;18:3558-3585.) Although colony-stimulating factors are not generally indicated for prophylactic use in cancer patients who receive chemotherapy that does not suppress the bone marrow, they may be used in patients who are at increased risk for febrile neutropenia or infection due to bone marrow compromise or their disease. Myeloma patients fall into this category, so use of CSFs is recommended even in cases where nonsuppressive chemotherapy is used.

Guidelines issued by the National Comprehensive Cancer Network (NCCN) in 2005 for use of colony-stimulating (myeloid) growth factors in cancer treatment concur with those issued by ASCO. NCCN recommends prophylactic use of growth factors in patients receiving treatment with curative intent, adjuvant therapy, or treatment expected to prolong survival and improve quality of life when there is a 20% or higher probability of developing febrile neutropenia or neutropenia that would compromise treatment (high risk). Growth factors should also be considered when there is a 10% to 20% probability of these events (intermediate risk).

Colony-stimulating factors are widely used to mobilize peripheral blood stem cells in patients with myeloma in preparation for stem cell transplant. However, the optimal method of mobilization in this patient population has not been defined.

The chemotherapeutic agent cyclophosphamide is most commonly used in combination with a CSF because of its ability to mobilize stem cells; it also provides some measure of disease control. Administration of melphalan and G-CSF has also been shown to be an effective mobilization regimen that also provided disease control in a small Phase II study involving 32 myeloma patients. (Gupta et al. *Bone Marrow Transpl.* 2005;35(5)441-7.)

Dosage and Administration

CSFs are administered as an injection under the skin or into a vein. The dose and schedule of administration varies with the individual agent and its specific use.

- When used in patients receiving chemotherapy, Leukine or Neupogen is typically given 24 to 72 hours following the completion of a cycle of chemotherapy and is continued daily for up to 2 weeks until neutrophil counts have risen to about 10,000 cells/mm^3. The next cycle of chemotherapy is given at least 24 hours after completion of CSF therapy. Neulasta is a long-acting form of filgrastim and is administered once per chemotherapy cycle at least 24 hours following the completion of chemotherapy.
- When used for stem cell mobilization, Leukine or Neupogen is given daily and stem cell collection is started when blood cell counts have risen to a sufficient level, usually by day 5. The colony-stimulating factor is continued during stem cell collection, which usually takes 1 to 3 days.
- When used following stem cell transplant, Leukine or Neupogen is usually started within a day of the infusion of stem cells and is continued until neutrophil counts have risen to about 1,000 to 1,500 cells/mm^3 for 3 consecutive days.

Recommended doses of these colony-stimulating factors are as follows:

- Neupogen: 5 mcg/kg/day when used to prevent febrile neutropenia during chemotherapy; 10 mcg/kg/day when used for stem cell mobilization
- Leukine: 250 mcg/m^2/day
- Neulasta: 6 mg once per chemotherapy cycle

Potential Side Effects

Colony-stimulating factors are generally well tolerated. The most common side effects, which may be related to the underlying disease or treatment, include flu-like symptoms, such as muscle and bone pain, slight fever, fatigue, weakness, or headache. Some slight redness or discomfort at the injection site might also be noted.

There have been rare reports of severe adverse events, including adult respiratory distress syndrome (inflammation of the lungs) and rupture of the spleen, in patients receiving Neulasta and Neupogen. In clinical trials of Leukine, there were occasional reports of fluid retention, shortness of breath, rapid heartbeat, and laboratory abnormalities (increases in creatinine, bilirubin, and liver enzymes).

Benefits of Colony-stimulating Factors in Cancer

Several randomized trials in patients receiving high-dose chemotherapy and stem cell transplantation have documented that colony-stimulating factors can

reduce:

- the severity of neutropenia
- the duration of neutropenia by up to a week
- the number of infectious complications
- the length of hospitalization
- the number of days of intravenous antibiotic treatment
- episodes of fever

Benefits of Colony-stimulating Factors in Myeloma

Infection is a frequent complication in myeloma, not only because of low neutrophil counts, but because there is reduced production of normal protective immunoglobulin, and the malignant plasma cells in the bone marrow crowd out other important immune cells. Therefore, any steps taken to reduce the possibility of infection are beneficial. In addition to the general benefits in cancer, use of CSFs in myeloma have been shown to

- reduce toxicity following high-dose melphalan therapy
- reduce the number of infections in myeloma patients post transplantation

Results of a study comparing the use of G-CSF (Neupogen) and GM-CSF (Leukine) in stem cell transplantation in myeloma showed that both were equally effective agents for mobilization of stem cells for harvest prior to transplant. (Arora et al. *Biol Blood Marrow Transplant*. 2004;10(6):395-404.

Several small studies have demonstrated that pegfilgrastim, the long-acting form of filgrastim, is equally effective as filgrastim in stem cell mobilization and recovery of white blood cells following autologous peripheral blood stem cell transplant in patients with myeloma. A single dose of pegfilgrastim (12 mg) was capable of mobilizing a sufficient number of stem cells for transplant with early engraftment and sustained hematological reconstitution in patients with myeloma (n=12), as was filgrastim (n=12), in a German study. (Steidl et al. *Bone Marrow Transplant.* 2005;35(1):33-6.) The same group demonstrated that a single 6-mg dose of pegfilgrastim is equally potent as a 12-mg dose for mobilization and harvest of peripheral blood stem cells in patients with myeloma (each dose, n=15). (Bruns et al. *Transfusion.* 2006;46(2):180-5.) Results of a Phase II study showed that, after high-dose chemotherapy and transplant, a single dose of pegfilgrastim (6 mg) administered 24 hours after transplant was comparable to daily filgrastim in patients with myeloma or lymphoma (n=38). (Jagasia et al. *Bone Marrow Transplant.* 2005;35(12):1165-9.) Time to neutrophil engraftment was comparable between the two agents.

New Growth Factors Under Investigation

Mozobil™ (plerixafor). Mozobil™ (plerixafor, AMD3100, AnorMED) is an investigational agent that increases the number of stem cells that can be collected prior to transplant. By blocking CXCR4, a specific cellular receptor, Mozobil triggers the rapid movement of stem cells out of the bone marrow and into the circulating blood. The efficacy of a mobilization regimen of Mozobil in combination with G-CSF is currently being compared with G-CSF alone in Phase III trials in patients with myeloma undergoing autologous transplant.

Preliminary data from a Phase II trial being conducted in patients with myeloma

(n=15) or non-Hodgkin's lymphoma (n=4) suggests that, in combination with G-CSF, Mozobil rapidly and predictably increases the number of CD34+ stem cells in the peripheral blood, which facilitates successful transplantations. (Flomenberg et al. *Blood.* 2005;106(5):1867-74.) In this study, mobilization treatment consisted of 5 days of G-CSF (10 µg/kg, subcutaneously in the morning) and a single dose of Mozobil (240 µg/kg, subcutaneously) in the evening of day 4, 10 to 11 hours prior to apheresis. As expected, following 4 days of G-CSF treatment, the CD34+ cell count in the peripheral blood increased 69-fold (range, 16-258-fold). Addition of Mozobil led to almost a tripling of circulating CD34+ cells within 10 hours after administration (2.7-fold increase, range 1.1-6.9). The mobilized cells appeared to be fully functional and Mozobil was well tolerated.

The CXCR4 receptor also appears to be an important regulator of migration in myeloma. In the laboratory, Mozobil inhibits migration and adhesion of myeloma cells, suggesting that evaluation of this agent as an inhibitor of homing of myeloma cells in clinical trials may be warranted. (Ghobrial et al. *Blood.* 2005;106(11). Abstract 2492.)

Reviewed by:

William I. Bensinger, MD
Member, Fred Hutchinson Cancer Research Center
Professor of Medicine, University of Washington